Amendments to the Drawings

Please delete drawing sheets 4 and 5.

REMARKS

Claims 1-29 are currently pending, claims 1-29 have been amended to recite "colorectal adenoma" or "colorectal carcinoma" where appropriate.

Drawings

Applicants have deleted FIG. 3a-e.

The description of the drawings has been revised to describe the current drawings. The descriptions in ¶ 13 and ¶ 14 have been amended to describe detection of "plasma" β-catenin RNA and "plasma" β-actin RNA as shown and described in ¶ 24. In ¶ 13 and ¶ 14, the descriptions of FIG. 2a-2e have been amended to include the term "plasma" β-catenin RNA. The term "plasma" β-catenin is used throughout the specification and is specifically supported in ¶ 24. The description of FIG. 2 has been amended in ¶ 14 to include "FIG. 2d and FIG. 2e illustrate detection of plasma β-catenin and β-actin RNA from healthy individuals using RT-PCR." FIG. 2d and FIG.2e are described in ¶ 24. ¶ 15 has been deleted. ¶ 31 has been amended to remove reference to FIG. 3.

These figures and descriptions were present in the original examples and no new matter is included.

Enablement

The Examiner has rejected the claims under §35 USC 112 as not enabled under *In re Wands*, 8 USPQ2d 1400.

Predictability – The Examiner argues that the biological and chemical arts are unpredictable. Applicants respectfully rebut this argument. The detection of RNA and DNA are routine in all biochemistry laboratories. The process of RNA and DNA detection has been automated and at present several companies offer automated systems for the detection of RNA and DNA.[1] RT-PCR has likewise been used without incident to quantify DNA and RNA

[1] Applied Biosystems Incorporated (ABI) at www.appliedbiosystems.com, bioMérieux at www.biomerieux.com, Qiagen at www.qiagen.com, and Roche at www.roche.com, among others.

concentrations blood serum and plasma.[2] Thus, given the gene of interest, beta-catenin, one of ordinary skill in the art can reliably and predictably assay samples for beta-catenin RNA and DNA.

Adenomas and Carcinomas – Applicants are well aware of the classification of cancerous tissues and pre-cancerous tissues. Standards have been put forth for the reference and classification of colorectal adenomas and carcinomas.[3] Colorectal carcinoma (CRC) arises from neoplastic adenomatous polyps,[4] and advanced adenomas exhibiting high-grade dysplasia are likely to develop into colorectal cancer.[5] Adenoma is considered a risk factor of colorectal cancer and as "pre-neoplastic colorectal polyps (adenomatous polyps)" as described in the Claims. Thus, the description of colorectal adenomas as pre-neoplastic polyps and colorectal carcinomas as cancer is correct.

Wong

The Wong reference (2004) is after-arising technology and is not prior art. The current application claims priority to PCT/US03/20587 filed June 27, 2003 and USSN 60/392,191 filed June 28, 2002. Applicants arguments and statements herein **do not** constitute an admission of prior art.

The Examiner states "Wong further proposes that a large-scale study would be needed to investigate whether plasma β-catenin mRNA might have a role in population screening for colorectal cancer (page 1616, col. 2)." The Examiner has selected one statement from Wong regarding the use of beta-catenin as a **population** screen. This one statement is a forward looking statement regarding one specific type of study. This statement is contrary to the reference as a whole, which concludes that β-catenin does provide a good and specific marker for

[2] Yan and Dennin, "A high frequency of GBV-C/HGV coinfection in hepatitis C patients in Germany," World J Gastroenterol. 2000 Dec;6:833-841; Rostaing, et al., "Changes in hepatitis C virus RNA viremia concentrations in long-term renal transplant patients after introduction of mycophenolate mofetil," Transplantation. 2000 Mar 15; 69(5):991-4.
[3] Jass and Sobin, "Histological Typing of Intestinal Tumors." *In:* International Histological Classification of Tumors. Geneva: World Health Organization, 1989.
[4] Leslie, et al., "The colorectal adenoma-carcinoma sequence." Br J Surg. 89:845–60 (2002).
[5] Shinya and Wolff, "Morphology, anatomic distribution and cancer potential of colonic polyps." Ann Surg. 190:679–683 (1979); Nusko et al., "Risk related surveillance following colorectal polypectomy." Gut. 51:424–8 (2002).

colorectal adenoma and colorectal carcinoma. Although Dr. Hsiao's name was not included in the Wong reference, Cesar Wong and Dr. Hsiao performed most of the published work in Wong et al. while Cesar Wong was working toward a Ph.D. degree under the supervision of Dr. Hsiao. Later, the work was published without Dr. Hsiao's permission and without recognition in the publication, thus Wong is the work of the current inventors. Nevertheless, the data in the reference support the conclusions in the current application and do not contradict or detract from the specification or claims.

Osmer

The Osmer reference (2006) is after-arising technology and is not prior art. Applicants arguments and statements herein **do not** constitute an admission of prior art.

Osmer et al, 2006 reported on "Novel blood biomarkers of human urinary bladder cancer". In the study, the authors employed **nucleated** blood cells for total RNA extraction. This is different than detecting extra-cellular β-catenin DNA or RNA in plasma or serum samples, as conducted in the current application. Applicants have demonstrated in the current application that the levels of β-catenin RNA or DNA in the plasma or serum is correlated with colorectal adenoma and carcinoma.

Fleischhacker

The Fleischhacker reference (2007) is after-arising technology and is not prior art. Applicants arguments and statements herein **do not** constitute an admission of prior art.

The Examiner argues "Fleischhacker teaches mRNA is higher in serum than plasma and that clinical data may contradict plasma mRNA concentrations." The Fleischhacker review is well understood by the Applicants. In Fleischhacker's review, he specifically had reservations applying circular DNA for clinical diagnosis because none of the biomarkers he cited, including the patented p53 or k-ras, yields high sensitivity. One of the examples relied on is PCT application WO0142504: Detection of extracellular tumor-associated nucleic acid in blood plasma or serum. In that the detection rate and the specificity are much lower than described in the current application. Fleischhacker is correct, based the Applicants' experiments and

observations, plasma will yield a greater amount of RNA and DNA than serum. Some of this may be attributed to handling as cellular RNA and DNA might be released from blood cells, especially if the blood samples have been sitting more than 7 or 8 hours at room temperature. To avoid the contamination of cellular RNA and DNA, fresh drawn plasma samples may be used. However, even under less than optimal conditions, serum is still a possible source as long as the procedure is performed correctly. Whether using plasma or serum, it will not affect the reported results in the present application because the results demonstrate conclusively with **strong statistical significance** that the **methods are enabled**. When comparing a patient's β-catenin plasma or serum RNA or DNA to known normal, colorectal adenoma, and colorectal carcinoma populations, the individual can be classified as having no neoplastic polyps, colorectal adenoma, or colorectal carcinoma with high probability. Fleischhacker's statements in the review are directed to a call for standardization in plasma and serum CNA quantification so that multiple studies may be compared to improve statistical significance. Fleischhacker does not detract from the individual studies or the conclusions drawn therein.

Guidance in the Specification

The specification describes methods of analyzing patient β-catenin RNA or DNA in the plasma or serum. If one of ordinary skill in the art were to use the methods described in the specification to detect β-catenin in patient plasma or serum they could determine whether the patient had no neoplastic polyps, colorectal adenoma, or colorectal carcinoma with high probability. That is the method described in the specification and recited in the claims.

Quantity of Experimentation

No experimentation is required to detect β-catenin in patient plasma or serum and determine whether the patient had no neoplastic polyps, colorectal adenoma, or colorectal carcinoma with high probability based on the methods provided in the specification and recited in the claims. Because the specification describes **working examples** where individuals were described in each of the categories, no neoplastic polyps, colorectal adenoma, or colorectal carcinoma, with high probability, the instant methods must be enabled.

The Examiner argues "The claims are broadly drawn to any patient … humans, dogs, and cats among other animals." It is well known by a person of ordinary skill in the art that the β-catenin, α-catenin, and E-cadherin genes are present at cellular junctions in animals. Because the genes and methods of detecting these genes are known in the art and their expression is correlated with that of humans, there is no unpredictable experimentation required to measure serum or plasma RNA or DNA in an animal of choice.

Serum – Example 5, in the provisional application, PCT application and described in ¶ 30 of the current application, **demonstrates detection** of beta-catenin DNA **in serum samples**. Thus Applicants have provided working examples detecting beta-catenin in patient serum enabling such methods.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Methods Sufficiently Enabled

Although different methods may be used to detect beta-catenin RNA and DNA, each providing different quantitative measurements, the applicants have demonstrated that, regardless of the method used to measure beta-catenin RNA or DNA:

1) normal patients without neoplastic tissues will have very low or no beta-catenin RNA or DNA in the plasma or serum,

2) patients with pre-neoplastic colorectal adenomas will have intermediate levels of beta-catenin RNA or DNA in the plasma or serum, and

3) patients with colorectal carcinomas will have high levels of beta-catenin RNA or DNA in the plasma or serum.

This conclusion is supported by the current application and Wong.

	USSN 10/516,864		Wong	
	Range	Median	Range	Median
Carcinoma	6700-44000	22000	1480-933,100	8737
Adenoma	690-1800	1100	541-2,254	1218
Normal	0-169	36	0-1,366	291

The Examiner has provided no examples that contradict the sufficiency of the disclosure or that the methods describe will not function as provided in the specification. In order to support a rejection for lack of enablement the Examiner must provide **reasonable evidence** that the disclosure is not enabling.[6] Applicants have provided **several working examples** of the invention using a variety of methods including PCR amplification, immunochemical staining, and RT-PCR. The specification is replete with evidence that the Applicant **was in possession** of the claimed invention and the methods are provided for one of skill in the art to practice the invention.[7] Although additional experimentation may be required to use other methods of detecting beta-catenin RNA or DNA, applicants have provided methods of analyzing levels of beta-catenin (¶ 41) detected in populations of normal, colorectal adenomas, or colorectal carcinoma and classifying a patient with respect to those populations as required for patentability.[8] While an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is **improper** for Office personnel to request evidence regarding the **degree of effectiveness**.[9]

[6] In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

[7] The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. 35 USC §112; The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973).

[8] The court reversed the findings of the district court for lack of clear and convincing proof that undue experimentation was needed. The court ruled that since one embodiment (stainless steel electrodes) and the method to determine dose/response was set forth in the specification, the specification was enabling. The question of time and expense of such studies, approximately $50,000 and 6-12 months standing alone, failed to show undue experimentation. In *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989)

[9] See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981)

Written Description

A) The Examiner has rejected claims 1-25 under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner states, "The claim is unclear whether the process merely requires detecting beta-catenin in the serum and plasma or whether the claim requires making the association between the presence of the nucleic acid and cancer." The claims currently recite "determining the presence of the colorectal cancer based on the detected presence of beta-catenin …" Thus the claims as drafted require correlation between the presence of "beta-catenin" RNA or DNA in order to determine the "presence of the colorectal cancer."

B) Claim 21 has been amended to recite "whereby the presence of high levels of beta-catenin is indicative of neoplastic disease."

C) "Approximately" is defined by the ratio described in the claims and the range of patient beta-catenin levels such that:

	USSN 10/516,864		Ratio
	Range	Median	Range / **(36)**
Carcinoma	6700-44000	22000	185-1225
Adenoma	690-1800	1100	20-50
Normal	0-169	**36**	0-5

Note that the claims as amended correctly describe the ratio as DNA or RNA measured in the patient to the relative amount in a control population. Thus there will never be a zero in the denominator and the calculation will be consistent for each measurement.

CONCLUSIONS

Applicants have clearly describes and claimed methods of determining the presence of "colorectal adenoma" or "colorectal carcinoma" by measuring serum and plasma beta-catenin RNA or DNA. Applicants have surpassed the standard of enablement required for patentability.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. No fees are believed due with this submission. If fees are required, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 50-3420, reference 32144183-000004 (MDB).

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